Two Syntheses of Pinane Thromboxane A_2

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The thromboxane analogue (PTA_2) (**2a**) has been synthesized from nopol (**3a**) and *via* conjugate addition of the cuprate (**18a**) to myrtenal (**17**).

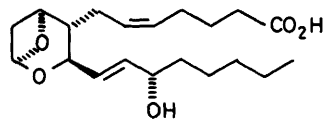
Thromoboxane A_2 (TXA_2) (**1**) is a naturally occurring unstable ($t_{\frac{1}{2}}$ 32 s at pH 7.4 and 37 °C) metabolite of the prostaglandin endoperoxide (PGH_2), with potent vasoconstricting and blood platelet aggregating properties.[1] We[2] and others[3] have briefly reported the synthesis of a stable TXA_2 analogue based on the pinane ring system (6,6-dimethylbicyclo[3.1.1]heptane) and we here describe this work in detail.

Our objective was to replace the oxygen functions of the cyclic acetal system in TXA_2[1] by their carbon equivalents to afford a stable molecule of similar geometrical shape, thus preserving the spatial disposition of the side-chain groupings which is considered to be important for retention of biological activity. We chose to synthesize an analogue based on the pinane ring system [*cf.* (**3a**)] because optically active pinane derivatives are readily available.

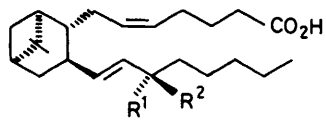
The commercially available pinane alcohol nopol (**3a**)[4] is an attractive starting material since it enables the β-chain of the thromboxane to be inserted *via* an *anti*-Markownikov addition to the ring double bond, and the α-chain to be constructed by extension of the 2-hydroxyethyl unit. Introduction of the β-chain was attempted by carbonylation of nopol by a borane and carbon monoxide in the presence of lithium tri-t-butoxyaluminium hydride and then Wittig elaboration of the resulting aldehyde. Attempts to form the desired borane derivative of nopol using 9-BBN (9-borabicyclo[3.3.1]nonane) (2 equiv.) failed, possibly because the bulky borinate, initially formed, sterically prevented further hydroboration. However, when the hydroxy group was protected as the tetrahydropyranyl (THP) ether (**3b**) the required aldehyde (**4a**) was obtained in 25% yield. Only one product was detected by t.l.c. and was assumed to have the desired all-*trans* configuration, as a consequence of the directing influence of the gem-dimethyl group and steric interaction with the 2-hydroxyethyl chain. This assignment accords with the known stereospecific hydroboration of α-pinene with 9-BBN and the fact that carbonylation of boranes is known to occur with retention of configuration.[5,6]

The aldehyde (**4a**), which was unstable, was subjected to cursory purification by column chromatography and then allowed to react with the sodio-derivative of dimethyl 2-oxoheptylphosphonate. Hydrolysis of the THP ether (**4b**) with acetic acid in aqueous tetrahydrofuran (THF) afforded the enone alcohol (**5a**) which was purified by column chromatography. It was apparent from the ^{13}C n.m.r. spectrum of compound (**5a**) that only one stereoisomer was present, confirming that the formation of (**4a**) had occurred stereospecifically. The non-stereospecific formation of (**4a**) would have led to a mixture of diastereoisomers which should be detectable by ^{13}C n.m.r. spectroscopy.

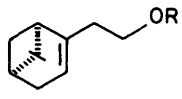
Oxidation of the enone alcohol (**5a**) using chromium trioxide and sulphuric acid in dimethylformamide (DMF) afforded the enone acid (**5b**). The latter was reduced with lithium tri-s-butylborohydride (L-Selectride) to give the hydroxy acid as a mixture of C-15 epimers† (**6a** and **b**) which were separated by column chromatography.



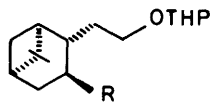
(1)



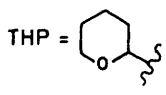
(2) a; R^1 = OH, R^2 = H
b; R^1 = H, R^2 = OH



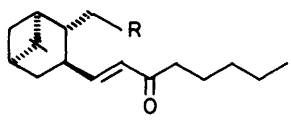
(3) a; R = H
b; R = THP



(4) a; R = CHO
b; R =
c; R = CH_2OH
d; R = CH_2OAc



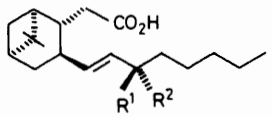
THP =



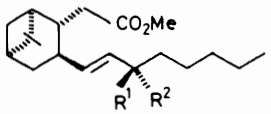
(5) a; R = CH_2OH
b; R = CO_2H

The diastereoisomers (**6a**) and (**6b**) were taken forward both separately and as a mixture. In the latter case the final products could be separated by h.p.l.c. (high-performance liquid chromatography). Esterification of the acids (**6a**) and (**6b**) with diazomethane afforded the hydroxy esters (**7a**) and (**7b**) which were then converted into their THP ethers (**7c**) and (**7d**). Reduction of the latter to the alcohols (**8a**) and (**8b**) by lithium aluminium hydride followed by oxidation using pyridinium chlorochromate afforded the aldehydes (**8c**) and (**8d**) which were treated with the ylide (**9**) to give the THP ethers (**10a**) and (**10b**). Initially the ylide (**9**) was generated using sodium

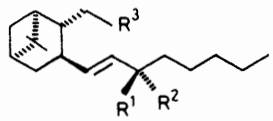
† Prostanoid numbering.



(6) a; R^1 = H, R^2 = OH
b; R^1 = OH, R^2 = H

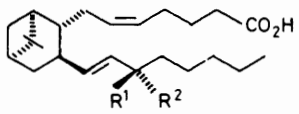


(7) a; R^1 = H, R^2 = OH
b; R^1 = OH, R^2 = H
c; R^1 = H, R^2 = OTHP
d; R^1 = OTHP, R^2 = H



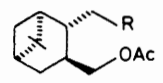
(8) a; R^1 = H, R^2 = OTHP, R^3 = CH_2OH
b; R^1 = OTHP, R^2 = H, R^3 = CH_2OH
c; R^1 = H, R^2 = OTHP, R^3 = CHO
d; R^1 = OTHP, R^2 = H, R^3 = CHO

(9) $(C_6H_5)_3P{=}CH[CH_2]_3CO_2K$

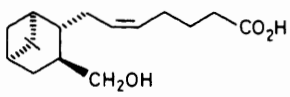


(10) a; R^1 = H, R^2 = OTHP
b; R^1 = OTHP, R^2 = H

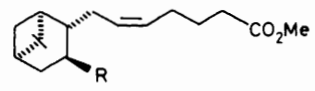
methylsulphinylmethanide in dimethyl sulphoxide[7] (DMSO) but in our hands the yields of acid (**10a** and **b**) were low and variable. However, the use of potassium t-butoxide in THF to generate the ylide gave consistent and reasonable yields. Hydrolysis of the THP ethers (**10a**) and (**10b**) then gave pinane thromboxane A_2 (PTA_2) (**2a**) and its C-15 epimer (**2b**). The oxidation of nopol (**3a**) to the corresponding aldehyde for elaboration as the acetal was also considered since this would obviate the need for protecting groups later in the synthesis. However, oxidation of nopol using pyridine–sulphur trioxide complex, pyridinium chlorochromate with or without a buffer, or pyridinium dichromate was always accompanied by migration of the endocyclic double bond into conjugation with the newly formed formyl group.



(11) a; R = CH_2OH
b; R = CHO

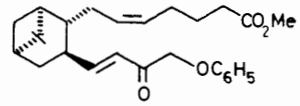


(12)

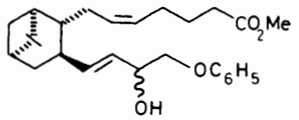


(13) a; R = CH_2OH
b; R = CHO

(14)

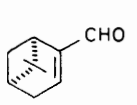


(15)

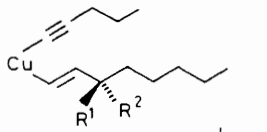


(16)

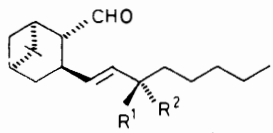
A modification of this synthesis was devised in which the side-chains were attached in the reverse order, permitting elaboration of the β-chain at a later stage, thus facilitating, as illustrated below, the synthesis of β-chain analogues from a common intermediate. The aldehyde (**4a**) was reduced with lithium aluminium hydride to the alcohol (**4c**) which was protected as the acetyl derivative (**4d**). Removal of the THP protecting group and oxidation of the alcohol (**11a**) with pyridinium chlorochromate afforded the aldehyde (**11b**). The latter, when treated with the ylide (**9**) with concurrent hydrolysis of the acetoxy group, gave the hydroxy acid (**12**). The methyl ester of the latter, compound (**13a**), was oxidised by pyridinium chlorochromate to the aldehyde (**13b**) which was successfully condensed with the ω-phenoxyphosphorane (**14**). Reduction (L-Selectride) of the product (**15**) gave a mixture of the hydroxy esters (**16**) epimeric at C-15.



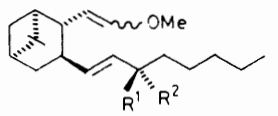
(17)



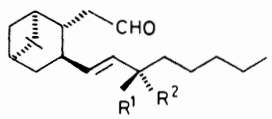
(18) a; R^1 = H, R^2 = OSi
b; R^1 = OSi, R^2 = H



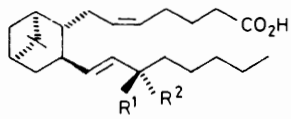
(19) a; R^1 = H, R^2 = OSi
b; R^1 = OSi, R^2 = H



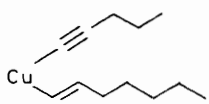
(20) a; R^1 = H, R^2 = OSi
b; R^1 = OSi, R^2 = H



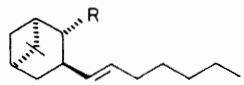
(21) a; R^1 = H, R^2 = OSi
b; R^1 = OSi, R^2 = H

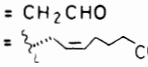


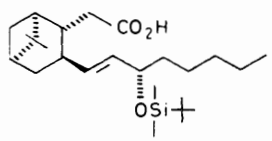
(22) a; R^1 = H, R^2 = OSi
b; R^1 = OSi, R^2 = H



(23)



(24) a; R = CHO
b; R = CH=CHOMe
c; R = CH_2CHO
d; R = 
e; R = CH_2CO_2H



(25)

Our second, shorter approach to PTA_2 (**2a**) afforded a totally stereospecific synthesis.* The commercially available αβ-

* This synthesis was also reported independently by Nicolaou and his co-workers.[3]

unsaturated aldehyde myrtenal (**17**) is a convenient starting material since a 1:4 cuprate addition of the β-chain followed by 1-carbon homologation of the aldehyde and chain extension would give PTA_2 (**2a**). Using the optically active cuprate reagent (**18a**), and exclusive addition to the β face of (**17**) a totally stereospecific synthesis was achieved.

Myrtenal (**17**) was coupled with the optically active cuprate (**18a**) using the method of Corey and Beames.[8] The resultant aldehyde (**19a**) was then extended by one methylene unit by Wittig condensation with the ylide generated from methoxymethylene(triphenyl)phosphonium chloride using lithium diisopropylamide, followed by cleavage of the *cis*/*trans*-vinyl ether (**20a**) with mercury(II) acetate and potassium iodide to give the aldehyde (**21a**). Wittig reaction between the ylide from (4-carboxybutyl)triphenylphosphonium bromide (**9**) and the aldehyde (**21a**), as described above for the synthesis of (**10a**) and (**10b**), followed by acid hydrolysis of the t-butyldimethylsilyl protecting group, afforded PTA_2 (**2a**).

The same synthetic route was followed using the cuprate (**23**) to give dehydroxy-ω-nor-PTA_2 (**24d**) and using (**18a**) and (**18b**) to give PTA_2 (**2a**) and its C-15 epimer (**2b**).

To allow a stereochemical comparison of the two syntheses the aldehyde (**21a**) from the 'myrtenal' route was oxidised to the acid (**25**) which was hydrolysed to the 'nopol' route intermediate (**6a**). The c.d. spectra of the latter compound from both sources were identical.[9]

Experimental

^1H and ^{13}C N.m.r. spectra were measured in $CDCl_3$ solution, unless otherwise noted, on Varian A-60D, EM360, or CFT 20 spectrometers. I.r. spectra were measured on thin films (liquids) or KBr discs (solids) on a Unicam SP 1000 spectrophotometer. U.v. spectra were measured in ethanol solution on a Carey 17 spectrophotometer. T.l.c. and column chromatographs were carried out using silica gel. L.p.l.c. refers to column chromatography on plate-grade silica gel with a slight air pressure (*ca.* 5 p.s.i.) applied.

(1R,5S)-6,6-*Dimethyl*-2-[2-(*tetrahydropyran*-2-*yloxy*)*ethyl*]-*bicyclo*[3.1.1]*hept*-2-*ene* (**3b**).—To a solution of (1*R*,5*S*)-2-(2-hydroxyethyl)-6,6-dimethylbicyclo[3.1.1]hept-2-ene (nopol) (**3a**) (61.6 g) in dichloromethane (20 ml) was added conc. hydrochloric acid (2 drops) and then dihydropyran (56 g, 0.66 mol) was added to the stirred mixture. The temperature rose to, and was maintained at, 60 °C (the dichloromethane evaporated during the addition). The reaction mixture was kept acidic (pH *ca.* 4) by the addition of conc. hydrochloric acid as required. After 3 h at 60 °C the reaction mixture was cooled and then added dropwise to vigorously stirred, ice-cooled, aqueous sodium hydroxide (2M; 90 ml). The product was extracted with diethyl ether, and the extract was dried (Na_2SO_4) and distilled to give the *THP ether* (**3b**) (74 g, 79%) as an oil, b.p. 160—167 °C at 14 mmHg (Found: C, 76.75; H, 10.6. $C_{16}H_{26}O_2$ requires C, 76.75; H, 10.5%); $\nu_{max.}$ 1 040 (O–C) and 980 cm^{-1} (C=C); δ_H (60 MHz) 5.25 (1 H, m, C=CH), 4.55 (1 H, m, OCHO), 3.7 (4 H, m, 2 × CH_2O), 1.1—2.5 (17 H, complex m), and 0.8 (3 H, s, CH_3).

(1S,2S,3S,5R)-3-*Formyl*-6,6-*dimethyl*-2-[2-(*tetrahydropyran*-2-*yloxy*)*ethyl*]*bicyclo*[3.1.1]*heptane* (**4a**).—To a stirred solution of the THP ether (**3b**) (12.6 g, 0.05 mol) in dried THF (40 ml) under nitrogen at room temperature was added dropwise a solution of 9-BBN (0.5M; 100 ml, 0.05 mol) in THF. The reaction mixture was stirred for 1 h at room temperature, and then for 18 h under reflux followed by cooling to −35 °C. The reaction vessel was flushed with carbon monoxide which was maintained at a slight positive pressure by means of a mercury trap. When carbon monoxide absorption had ceased (*ca.* 0.5 h) a solution of lithium tri-t-butoxyaluminium hydride (12.7 g, 0.05 mol) in dried THF (50 ml) was added dropwise during 45 min, a positive carbon monoxide pressure being maintained throughout. The reaction mixture was stirred for 1.5 h at −35 °C and was then allowed to warm to room temperature during 1 h. A pH 7 phosphate buffer (2.2M in K_2HPO_4 and NaH_2PO_4; 120 ml) was added followed by dropwise addition of aqueous hydrogen peroxide (30%; 22 ml) with ice–salt-bath cooling. After being stirred for 0.5 h the reaction mixture was diluted with brine (100 ml). The upper (organic) layer was washed with brine (100 ml), dried (Na_2SO_4), and evaporated under reduced pressure to give a milky white oil which was chromatographed on a column (34 mm × 40 cm) of silica gel with n-hexane–diethyl ether (5:1) as eluant to give the aldehyde (**4a**) (3.5 g, 25%) as a pale yellow oil, R_F (diethyl ether) 0.54; $\nu_{max.}$ 2 750 and 1 728 (CHO), and 1 040 cm^{-1} (O–C–O); δ_H (80 MHz) 9.65 (1 H, m, CHO), 4.52 (1 H, m, OCHO), 3.25—4.0 (4 H, 2 × CH_2O), and 0.6—2.8 (22 H, complex m). This compound was unstable and was used immediately.

(1S,2R,3R,5S)-6,6-*Dimethyl*-3-[(1(E)-3-*oxo*-*oct*-1-*enyl*]-2-[2-(*tetrahydropyran*-2-*yloxy*)*ethyl*]*bicyclo*[3.1.1]*heptane* (**4b**).—A stirred suspension of sodium hydride (0.12 g, 5.0 mmol) in dry THF (75 ml) under nitrogen was treated with a solution of dimethyl (2-oxoheptyl)phosphonate (1.0 g, 4.5 mmol) in dry THF (30 ml), and the mixture was stirred for 1.5 h by which time evolution of hydrogen had ceased. A solution of the aldehyde (**4a**) (1.2 g, 4.3 mmol) in dry THF (30 ml) was added dropwise. The reaction mixture was stirred for 2.5 h, then concentrated under reduced pressure and diluted with diethyl ether (100 ml) and the ether layer was washed with water (3 × 70 ml), dried (Na_2SO_4), and worked up to give an oil (1.3 g). Chromatography on a column of silica gel (2.4 × 30 cm) with n-hexane–diethyl ether (5:1) as eluant afforded the *enone* (**4b**) (0.68 g, 43%) as a pale yellow oil (Found: C, 76.5; H, 10.8%; M^+, 376. $C_{24}H_{40}O_3$ requires C, 76.55; H, 10.71%; *M*, 376); R_F [diethyl ether–ethyl acetate–n-hexane (3:1:1)] 0.58; $\lambda_{max.}$ (EtOH) 230 nm (ε 14 700); $\nu_{max.}$ 1 695 and 1 675 (conj. C=O), 1 625 (conj. C=C), and 1 030 cm^{-1} (O–CH–O); δ_H (60 MHz) 6.75 (1 H, dd, *J* 7 and 15.5 Hz, C*H*=CH–C=O), 5.97 (1 H, d, *J* 15.5 Hz, C=C*H*–C=O), 4.5 (1 H, m, OCHO), 3.6 (4 H, m, 2 × CH_2O), 0.8—2.8 (30 H, m), and 1.1 (3 H, s, CH_3).

(1S,2R,3R,5S)-2-(2-*Hydroxyethyl*)-6,6-*dimethyl*-3-[(E)-3-*oxo*-*oct*-1-*enyl*]*bicyclo*[3.1.1]*heptane* (**5a**).—A solution of the enone (**4b**) (0.9 g, 2.4 mmol) in glacial acetic acid (18 ml), water (9 ml), and THF (1.8 ml) was stirred at 45 °C for 4 h. The cooled mixture was extracted with diethyl ether, and the extract was washed in turn with water and saturated aqueous sodium hydrogen carbonate and dried (Na_2SO_4) to give, after work-up, the *enone alcohol* (**5a**) (0.67 g, 95%). A sample (0.15 g) was purified by column chromatography on a silica gel (15 g) column (11 × 2.4 cm) with diethyl ether–n-hexane (1:1) as eluant (0.1 g) (Found: C, 78.1; H, 11.2. $C_{19}H_{32}O_2$ requires C, 78.03; H, 11.03%); R_F [diethyl ether–n-hexane (1:1)] 0.15; $\lambda_{max.}$ (EtOH) 230 nm (ε 13 200); $\nu_{max.}$ 3 420 (OH), 1 690 and 1 670 (conj. C=O), 1 620 (conj. C=C), and 980 cm^{-1} (C=C); δ_H (60 MHz) 6.75 (1 H, dd, *J* 15.5 and 7 Hz, C*H*=CH–C=O), 6.0 (1 H, d, *J* 15.5 Hz, C=C*H*–C=O), 3.6 (2 H, t, *J* 7 Hz, CH_2OH), and 0.7—2.8 (28 H, complex m); δ_C 191.01 (s, C=O), 153.66 (d, *C*=C–C=O), 127.65 (d, C=*C*–C–O), 61.13 (t, CH_2OH), 44.83, 43.66, 41.31, 40.43, 39.36, 38.68, 33. 86, 31.54, 28.07, 24.03, 22.99, 22.50, and 13.92 p.p.m. (q, CH_3).

(1S,2R,3R,5S)-2-(*Carboxymethyl*)-6,6-*dimethyl*-3-[(E)-3-*oxo*-*oct*-1-*enyl*]*bicyclo*[3.1.1]*heptane* (**5b**).—Chromium triox-

ide (1.84 g, 18 mmol) was added to a stirred solution of the enone alcohol (**5a**) (0.70 g, 2.4 mmol) in DMF (14.5 ml) at room temperature during 0.5 h. After a further 0.5 h the mixture was cooled to 5 °C and was treated dropwise with a solution of conc. sulphuric acid (1.42 ml) in DMF (45 ml). The mixture was then stirred for 1.5 h and diluted with diethyl ether (40 ml) and the supernatant liquid was decanted from the insoluble material. The ethereal solution was washed with water (3 × 50 ml), dried (Na_2SO_4), and concentrated under reduced pressure to give the *enone acid* (**5b**) (0.64 g, 87%) as a yellow semi-solid. A sample was recrystallised from n-hexane to give a white crystalline solid, m.p. 73—74 °C (Found: C, 74.3; H, 9.8. $C_{19}H_{30}O_3$ requires C, 74.5; H, 9.87%); R_F (diethyl ether) 0.60; $\lambda_{max.}$(EtOH) 229 nm (ε 13 640); $\nu_{max.}$ 1 710 (CO_2H), 1 690 and 1 670 (conj. C=O), 1 620 (conj. C=C), and 980 cm^{-1} (C=C); δ_H (80 MHz) 6.7 (1 H, dd, *J* 15.5 and 7 Hz, CH=C), 5.9 (1 H, d, *J* 15.5 Hz, C=CH–C=O), 4.2 (1 H, br, CO_2H), and 0.75—2.7 (27 H, complex m); δ_C 191.1 (s, C=O), 178.6 (s, CO_2H), 152.2 (d, *C*=C–C=O), 128.3 (d, C=*C*–C=O), 45.0, 43.4, 41.1, 40.2, 39.8, 38.5, 34.0, 33.7, 31.5, 24.0, 22.5, 28.0 (q), 22.8 (q), and 13.9 p.p.m. (q).

(1S,2R,3R,5S)-2-(*Carboxymethyl*)-3-[(E)-3-*hydroxyoct*-1-*enyl*]-6,6-*dimethylbicyclo*[3.1.1]*heptane* (**6a** *and* **b**).—A solution of the enone acid (**5b**) (0.60 g, 20 mmol) in dried THF (2 ml) was added to a stirred solution of L-Selectride (1M; 3.9 ml, 3.9 mmol) in THF at −70 °C under nitrogen. The mixture was stirred for 0.5 h at −70 °C, then for 2.5 h at room temperature, cooled to 0 °C, and treated with aqueous sodium hydroxide (3M; 3 ml). Aqueous hydrogen peroxide (30%; 2 ml) was added cautiously and the mixture was stirred for 0.5 h, diluted with water (15 ml), washed with diethyl ether (20 ml), and acidified to pH 3 with aqueous hydrochloric acid (2M). Extraction with diethyl ether and drying (Na_2SO_4) the extract then evaporation of the solvent gave the products (**6a** and **b**) (0.31 g, 50%). Chromatography on a silica gel column (3.4 × 20 cm) with diethyl ether–ethyl acetate–n-hexane (3:1:1) as eluant gave (1S,2R,3R,5S)-2-(*carboxymethyl*)-3-[(E, 3S)-3-*hydroxyoct*-1-*enyl*]-6,6-*dimethylbicyclo*[3.1.1]*heptane* (**6a**) (0.12 g, 38%) (faster moving component) as an oil (Found: C, 73.6; H, 11.0%; M^+, 308. $C_{19}H_{32}O_3$ requires C, 73.98; H, 10.5%; *M*, 308); R_F [ethyl acetate–cyclohexane–formic acid (40:40:1)] 0.52; $\nu_{max.}$ 2 500—3 600 (CO_2H), 1 710 (CO_2H), and 970 cm^{-1} (C=C); δ_H (80 MHz) 5.2 (2 H, br, OH), 5.4 (2 H, m, CH=CH), 4.1 (1 H, br, C*H*OH), and 0.7—2.7 (27 H, complex m); δ_C 178.8 (s, CO_2H), 138.3 (d, C=*C*–C–OH), 131.5 (d, *C*=C–C–OH), 72.75 (d, C=C–*C*–OH), 45.2, 44.5, 41.5, 39.75, 38.8, 38.62, 37.2, 34.8, 34.3, 31.8, 28.1, 25.2, 22.8, 22.6, and 14.0 p.p.m. and (1S,2R,3R,5S)-2-(*carboxymethyl*)-3-[(E, 3R)-3-*hydroxyoct*-1-*enyl*]-6,6-*dimethylbicyclo*[3.1.1]*heptane* (**6b**) (0.13 g, 42%) as a white crystalline solid, m.p. 103—104 °C (Found: C, 73.6; H, 10.4%; *M*, 308); R_F [ethyl acetate–cyclohexane–formic acid (40:40:1)] 0.47; $\nu_{max.}$ (KBr) 2 600—3 320 (CO_2H), 1 690 (CO_2H), and 970 cm^{-1} (C=O); δ_H (80 MHz) 6.1 (2 H, br, OH), 5.4 (2 H, m, CH=CH), 4.1 (1 H, br, CHOH), and 0.7—2.7 (27 H, complex m); δ_C 177.5 (s, CO_2H), 139.6 (d, C=*C*–C–OH), 131.3 (d, *C*=C–C–OH), 73.55 (d, C=C–*C*–OH), 46.4, 44.8, 41.45, 40.8, 39.0, 38.6, 36.9, 35.05, 34.4, 31.7, 28.1, 25.1, 22.8, 22.6, and 14.0 p.p.m.

(1S,2R,3R,5S)-3-[(E)-3-*Hydroxyoct*-1-*enyl*]-2-(*methoxycarbonylmethyl*-6,6-*dimethylbicyclo*[3.1.1]*heptane* (**7a** *and* **b**).—A solution of the acid (**6a**) (0.5 g) in diethyl ether (15 ml) was treated with an ethereal solution of diazomethane until the characteristic green-yellow colour remained and nitrogen evolution ceased. After 1 h the excess of diazomethane was destroyed by the addition of acetic acid. The ethereal solution was washed with saturated aqueous sodium hydrogen carbonate, dried (Na_2SO_4), and concentrated to give the *ester* (**7a**) (0.47 g, 80%) (Found: C, 74.3; H, 11.0%; M^+, 322. $C_{20}H_{34}O_2$ requires C, 74.5; H, 10.6%; *M*, 322); R_F [diethyl ether–n-hexane (1:1)] 0.27; $\nu_{max.}$ 3 430 (OH), 1 738 (CO_2CH_3), and 970 cm^{-1} (C=C); δ_H (80 MHz) 5.4 (2 H, m, CH=CH), 4.05 (1 H, br, C*H*OH), 3.9 (3 H, s, CO_2CH_3), and 0.7—2.7 (28 H, complex m).

Similarly, the acid (**6b**) afforded the *ester* (**7b**) (0.9 g, 78%) (Found: C, 74.3; H, 10.9%; M^+, 322); R_F [diethyl ether–n-hexane (1:1)] 0.18; $\nu_{max.}$ 3 430 (OH), 1 738 (CO_2CH_3), and 970 cm^{-1} (C=C); δ_H (80 MHz) 5.4 (2 H, m, CH=CH), 4.05 (1 H, br, C*H*OH), 3.9 (3 H, s, CO_2CH_3), and 0.7—2.7 (28 H, complex m).

(1S,2R,3R,5S)-2-(*Methoxycarbonylmethyl*)-6,6-*dimethyl*-3-[(E)-3-(*tetrahydropyran*-2-*yloxy*)*oct*-1-*enyl*]*bicyclo*[3.1.1]*heptane* (**7c** *and* **d**).—To a stirred mixture of the hydroxy ester (**7a**) (0.2 g, 0.62 mmol), dichloromethane (2 ml), and conc. hydrochloric acid (1 drop) at 40 °C was added, dropwise, dihydropyran (110 mg, 1.3 mmol). After 3 h the mixture was added to vigorously stirred, ice-cooled aqueous sodium hydroxide (2M; 0.3 ml) and extracted with diethyl ether (3 × 10 ml). The extracts were washed with water, dried (Na_2SO_4), and concentrated to give the THP ether (**7c**) (0.23 g, 92%) as a pale yellow oil. An analytical sample (50 mg) was purified by l.p.l.c. on a column of silica gel (16 g, 2.4 × 14 cm) using diethyl ether–n-hexane (1:1) as eluant to give the THP ether (**7c**) (29 mg) as an oil (Found: M^+, 406. $C_{25}H_{42}O_4$ requires *M*, 406); R_F [diethyl ether–n-hexane (1:1)] 0.51; $\nu_{max.}$ 1 740 (CO_2CH_3), 1 020 (O–C–O), and 970 cm^{-1} (C=C); δ_H (80 MHz) 4.9—5.8 (2 H, br, CH=CH), 4.7 (1 H, m, OCHO), 3.2—4.3 (3 H, m, CH_2O and CHO), 3.65 (3 H, s, CO_2CH_3), and 0.7—2.8 (33 H, complex m).

Similarly, the hydroxy ester (**7b**) afforded *THP ether* (**7d**) as a yellow oil. A sample (80 mg) was purified by l.p.l.c. on a column of silica gel (16 g, 2.4 × 14 cm) using diethyl ether–n-hexane (1:1) as eluant to give (**7d**) (50 mg) as an oil (Found: C, 74.0; H, 10.7%; M^+, 406. $C_{25}H_{42}O_4$ requires C, 73.8; H, 10.4; *M*, 406); R_F [diethyl ether–n-hexane (1:1)] 0.47. The spectral properties (m.s., i.r., and n.m.r.) were as described for (**7c**).

(1S,2R,3R,5S)-2-(2-*Hydroxyethyl*)-6,6-*dimethyl*-3-[(E,3S)-3-(*tetrahydropyran*-2-*yloxy*)*oct*-1-*enyl*]*bicyclo*[3.1.1]*heptane* (**8a**).— A stirred suspension of lithium aluminium hydride (0.25 g, 0.62 mmol) in dried THF (6 ml) was treated dropwise with a solution of the THP ether (**7c**) (0.25 g, 0.62 mmol). After 4.5 h aqueous THF (1:1; 4 ml) was carefully added to destroy the excess of hydride and the aqueous layer was extracted with diethyl ether. The combined organic material was dried (Na_2SO_4) and concentrated to give the alcohol (**8a**) (0.23 g, 98%) as a yellow oil. An analytical sample (30 mg) was purified by t.l.c. on 3 analytical plates (20 × 20 × 0.025 cm) using diethyl ether–n-hexane (1:1) as the solvent system to give the *alcohol* (**8a**) (20 mg) (Found: C, 76.1; H, 10.9%; M^+, 378. $C_{24}H_{42}O_3$ requires C, 76.1; H, 11.2%; *M*, 378); R_F [diethyl ether–n-hexane (1:1)] 0.31; $\nu_{max.}$ 3 430 (OH), 1 020 (O–C–O), and 970 cm^{-1} (C=C); δ_H (80 MHz) 5.6 (1 H, dd, *J* 15 and 8 Hz, C*H*=CH), 5.1 (1 H, dd, *J* 15 and 8 Hz, CH=C*H*), 4.7 (1 H, m, OCHO), 3.0—4.2 (6 H, complex m, CHO, OH, and CH_2O), and 0.7—2.6 (33 H, complex m).

(1S,2R,3R,5S)-2-(2-*Hydroxyethyl*)-6,6-*dimethyl*-3-[(E,3R)-3-(*tetrahydropyran*-2-*yloxy*)*oct*-1-*enyl*]*bicyclo*[3.1.1]*heptane* (**8b**).—Similarly, the THP ether (**7d**) (0.90 g, 2.2 mmol) in dried THF (24 ml) was reduced using lithium aluminium hydride (0.10 g, 2.6 mmol) in dried THF (24 ml) to give an oil (0.98 g). This was purified by l.p.l.c. on a column of silica gel (16 g, 2.4 × 16 cm) using diethyl ether–n-hexane (1:1) as eluant to give the alcohol (**8b**) (0.49 g, 58%) as an oil, R_F [diethyl ether–n-hexane (1:1)] 0.24. Spectral properties (i.r., m.s., and n.m.r.) were as described for (**8a**).

(1S,2R,3R,5S),-2-(*Formylmethyl*)-6,6-*dimethyl*-3-[(E)-3-(*tetrahydropyran*-2-*yloxy*)*oct*-1-*enyl*]*bicyclo*[3.1.1]*heptane* (**8c** *and* **d**).—A stirred suspension of pyridinium chlorochromate (203 mg, 0.96 mmol) and sodium acetate (14.6 mg, 0.18 mmol) in dried dichloromethane (6 ml) was treated, in one aliquot, with a solution of the alcohol mixture (**8a** and **b**) (227 mg, 0.62 mmol) in dried dichloromethane (6 ml). The mixture was stirred for 1.5 h and then diluted with anhydrous diethyl ether and filtered. The product (130 mg) was purified by preparative t.l.c. (p.l.c.) (silica gel; 20 × 20 × 0.1 cm) using diethyl ether–ethyl acetate–n-hexane (3:1:1) to give the aldehyde mixture (**8c** and **d**) (80 mg, 40%); R_F [diethyl ether–ethyl acetate–n-hexane (3:1:1)] 0.59; $\nu_{max.}$ 2 600 and 1 730 (CHO), 1 020 (O–C–O), and 975 cm^{-1} (C=C); δ_H (60 MHz) 9.8 (1 H, t, *J* 1.5 Hz, CHO), 5.6 (1 H, dd, *J* 15 and 8 Hz, CH=C), 5.1 (1 H, dd, *J* 15 and 8 Hz, C=CH), 4.7 (1 H, m, OCHO), 3.0—4.2 (3 H, complex m, CHO and CH_2O), and 0.7—2.8 (43 H, complex m).

(1S,SR,3R,5S)-2-(*Formylmethyl*)-6,6-*dimethyl*-3-[(E,3S)-3-(*tetrahydropyran*-2-*yloxy*)*oct*-1-*enyl*]*bicyclo*[3.1.1]*heptane* (**8c**).—Following the procedure for the preparation of (**8c** and **d**) the alcohol (**8a**) (0.21 g, 0.56 mmol) in dried dichloromethane (6 ml) was oxidised using pyridinium chlorochromate (0.20 g, 0.95 mmol) in dried dichloromethane (6 ml) buffered by sodium acetate (14 mg) to give the aldehyde (**8c**) (0.20 g, 96%) with the same spectral properties (i.r., n.m.r.) as (**8c** and **d**); R_F [diethyl ether–ethyl acetate–n-hexane (3:1:1)] 0.58.

(1S,2R,3R,5S)-2-(*Formylmethyl*)-6,6-*dimethyl*-3-[(E,3R)-3-(*tetrahydropyran*-2-*yloxy*)*oct*-1-*enyl*]*bicyclo*[3.1.1]*heptane* (**8d**).—Following the procedure for the preparation of (**8c** and **d**) the alcohol (**8b**) (0.21 g, 0.56 mmol) in dried dichloromethane (6 ml) was oxidised using pyridinium chlorochromate (0.20 g, 0.95 mmol) in dried dichloromethane (6 ml) buffered by sodium acetate (14 mg) to give the *aldehyde* (**8d**) (0.2 g, 96%) with the same spectral properties (i.r., n.m.r.) as described for (**8c** and **d**) (Found: C, 76.5; H, 10.9%; M^+, 376. $C_{24}H_{46}O_3$ requires C, 76.55; H, 10.7; *M*, 376); R_F [diethyl ether–ethyl acetate–n-hexane (3:1:1)] 0.61.

(1S,2R,3R,5S)-2-[(Z)-6-*Carboxyhex*-2-*enyl*]-6,6-*dimethyl*-3-[(E)-3-(*tetrahydropyran*-2-*yloxy*)*oct*-1-*enyl*]*bicyclo*[3.1.1]*heptane* (**10a** *and* **b**).—Sodium hydride (50% in oil; 41 mg, 0.85 mmol) under nitrogen was washed twice with dried n-pentane (5 ml) and then suspended in dried DMSO (2 ml). The mixture was then stirred at 65—70 °C under nitrogen until gas evolution had ceased. The mixture, at 10 °C, was treated dropwise with a solution of (4-carboxybutyl)triphenylphosphonium bromide (0.25 g, 0.58 mmol) in dried DMSO (2 ml). The mixture was stirred at room temperature for 15 min, during which time the solution became a deep cherry red colour, and was then treated with a solution of the aldehyde (**8c** and **d**) (70 mg, 0.19 mmol) in dried DMSO (2 ml) in one portion, and the reaction mixture was stirred for 3 h under nitrogen. The reaction mixture was then added to vigorously stirred crushed ice (5 g), and the resulting aqueous mixture was washed with a mixture of diethyl ether and ethyl acetate (1:1; 10 ml), then adjusted to pH 4 by treatment with hydrochloric acid (2M), and extracted with diethyl ether (2 × 25 ml). The combined extracts were dried (Na_2SO_4) and concentrated to give the crude acid (**10a** and **b**) (60 mg) which was used without purification, $\nu_{max.}$ 2 300—3 600 (CO_2H), 1 710 (CO_2H), and 970 cm^{-1} (C=C); δ_H (80 MHz) 6.7 (1 H, br, OH), 5.3 (4 H, br complex m, CH=CH), 4.75 (1 H, br s, O–CH–O), 3.95 (2 H, m, OCH_2), 3.55 (1 H, m, CHO), and 0.7—2.7 (39 H, m).

(1S,2R,3R,5S)-2-[(Z)-6-*Carboxyhex*-2-*enyl*]-3-[(E)-3-*hydroxyoct*-1-*enyl*]-6,6-*dimethylbicyclo*[3.1.1]*heptane* (**2a** *and* **b**).—The crude acid (**10a** and **b**) (60 mg, 0.13 mmol) was dissolved in a mixture of water, glacial acetic acid, and THF (35:65:10; 2 ml) and the mixture was stirred at 40—45 °C for 3 h. The reaction mixture was diluted with diethyl ether and water and the separated organic phase was washed with water several times until the washings had pH 5. The organic material was dried (Na_2SO_4) and concentrated under reduced pressure to give a pale yellow oil (35 mg) which was purified by p.l.c. (silica gel; 20 × 20 × 0.1 cm) using ethyl acetate–cyclohexane–formic acid (40:40:1) as the developing solvent. This gave a mixture of PTA_2 and its C-15 epimer (**2a** and **b**) (18.5 mg, 25% for the last two stages) as an oil (Found: M^+, 376. $C_{24}H_{40}O_3$ requires *M*, 376); $\nu_{max.}$ 1 715 (CO_2H) and 980 cm^{-1} (C=C); δ_H (80 MHz) 7.1 (2 H, m, OH), 5.3 (4 H, m, CH=CH), 4.1 (1 H, m, C*H*OH), and 0.5—2.8 (33 H, m).

(1S,2R,3R,5S)-2-[(Z)-6-*Carboxyhex*-2-*enyl*]-6,6-*dimethyl*-3-[(E,3S)-3-(*tetrahydropyran*-2-*yloxy*)*oct*-1-*enyl*]*bicyclo*[3.1.1]*heptane* (**10a**).—A stirred suspension of (4-carboxybutyl)-triphenylphosphonium bromide (0.95 g, 2.1 mmol) in dried THF (20 ml) under argon was treated with a solution of potassium t-butoxide (0.61 g, 5.4 mmol) in dried THF (10 ml) at room temperature. After the reaction mixture had been stirred for 20 min a solution of the aldehyde (**8c**) (200 mg, 0.53 mmol) in dried THF (4 ml) was added. After the reaction mixture had been stirred for 2.5 h, water (7.4 ml) was added and the mixture was stirred for a further 0.5 h. The reaction mixture was washed with diethyl ether (20 ml) and the ether was extracted with saturated aqueous sodium hydrogen carbonate (20 ml). The combined aqueous fractions were acidified to pH 2 using dil. hydrochloric acid and then extracted with diethyl ether (2 × 30 ml). The combined organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure to give the acid (**10a**) (0.15 g) with the same spectral properties (i.r., n.m.r.) as for (**10a** and **b**). The product was used without further purification.

(1S,2R,3R,5S)-2-[(Z)-6-*Carboxyhex*-2-*enyl*]-6,6-*dimethyl*-3-[(E,3R)-3-(*tetrahydropyran*-2-*yloxy*)*oct*-1-*enyl*]*bicyclo*[3.1.1]*heptane* (**10b**).—Following the procedure for the preparation of (**10a**) the aldehyde (**8d**) (0.20 g, 0.53 mmol) in dried THF (4 ml) was treated with the ylide generated by treating (4-carboxybutyl)triphenylphosphonium bromide (0.953 g, 2.15 mmol) in dried THF (20 ml) with potassium t-butoxide (0.614 g, 5.4 mmol) in dried THF (14 ml) to give the crude acid (**10b**) (0.205 g) with the same spectral properties (i.r., n.m.r.) as (**10a** and **b**). This was used without further purification.

(1S,2R,3R,5S)-2-[(Z)-6-*Carboxyhex*-2-*enyl*]-3-[(E,3S)-3-*hydroxyoct*-1-*enyl*)-6,6-*dimethylbicyclo*[3.1.1]*heptane* (**2a**) (PTA_2).—Following the procedure for the preparation of (**2a** and **b**) the acid (**10a**) (150 mg, 0.33 mmol) was hydrolysed using a (35:65:10) mixture of water, glacial acetic acid, and THF (6 ml) to give the crude product (115 mg). A sample (16 mg) was purified by h.p.l.c. using n-hexane–ethyl acetate–acetic acid (700:50:5) to give PTA_2 (**2a**) (10.3 mg) as an oil (Found: M^+, 376. $C_{24}H_{40}O_4$ requires *M*, 376); $\nu_{max.}$ 2 300—3 600 (CO_2H), 1 710 (CO_2H), and 970 cm^{-1} (C=C); δ_H (400 MHz) 5.49—5.53 (2 H, complex m, CH=CH; 5.51 d of d, *J* 15.5 and 9.0 Hz, C*H*=CH–CHOH), 5.32—5.38 (2 H, complex m, CH=CH; 5.35 d of d, *J* 15.5 and 7.0 Hz, CH=C*H*–CHOH), 4.12 (d of t, *J* 7 and 9.0 Hz), 1.25—2.4 (23 H, m), 1.2 (3 H, s, CH_3), 1.06 (3 H, s), 0.89 (3 H, t, *J* 7.0 Hz, CH_2CH_3), and 0.76 (1 H, d, *J* 9.5 Hz, H*).

(1S,2R,3R,5S)-2-[(Z)-6-*Carboxyhex*-2-*enyl*]-3-[(E,3R)-3-*hydroxyoct*-1-*enyl*)-6,6-*dimethylbicyclo*[3.1.1]*heptane* (**2b**).—Following the procedure for the preparation of the isomeric mixture (**2a** and **b**) the acid (**10b**) (0.2 g, 0.44 mmol) was

* This is the 7-β-H of the pinane ring.

hydrolysed using a (35:65:10) mixture of water, glacial acetic acid, and THF (6 ml) to give a crude product (0.16 g). A sample (80 mg) was purified using l.p.l.c. on a column of silica gel (16 g, 2.4 × 16 cm) using diethyl ether–ethyl acetate–n-hexane (3:1:1) as eluant to give the *acid* (**2b**) (26 mg, 32%) as an oil (Found: C, 76.4; H, 10.9%; M^+, 376. $C_{24}H_{40}O_3$ requires C, 76.6; H, 10.7%; *M*, 376); $\nu_{max.}$ 2 300—3 600 (CO_2H), 1 710 (CO_2H), and 970 cm^{-1} (C=C); [h.p.l.c. n-hexane–ethyl acetate–acetic acid (700:50:50) (K^1 6.1)]; δ_H (400 MHz) 5.55 (1 H, d of d, *J* 15.5 and 8.5 Hz, C*H*=CHCHOH), 5.29—5.48 (2 H, m, CH=CH; 5.38 d of d, *J* 15.5 and 6.5 Hz, CH=C*H*CHOH) 4.12 (1 H, d of t, *J* 6.5 and 6.5 Hz, CHO), 1.25—2.40 (23 H, m), 1.20 (3 H, s, CH_3) 1.05 (3 H, s, CH_3), 0.89 (3 H, t, *J* 7.0 Hz, CH_2CH_3), and 0.78 (1 H, d, 9.5 Hz, H*).

(1S,2R,3S,5R)-3-*Hydroxymethyl*-6,6-*dimethyl*-2-[2-(*tetrahydropyran*-2-*yloxy*)*ethyl*]*bicyclo*[3.1.1]*heptane* (**4c**).—A stirred solution of the aldehyde (**4a**) (3.4 g, 12.5 mmol) in dried THF (20 ml) was treated with a solution of lithium aluminium hydride (0.50 g, 13 mmol) in dried THF (20 ml) at such a rate as to maintain a gentle reflux. The mixture was stirred for 1 h and a mixture of water (5 ml) in THF (10 ml) was added dropwise to destroy the excess of hydride and the mixture was extracted with diethyl ether. The extract was dried ($MgSO_4$) and concentrated under reduced pressure to give a light brown oil (2.4 g). The crude material was purified by l.p.l.c. on a column of silica gel (16 g, 2.4 × 14 cm) using diethyl ether as eluant to give the *alcohol* (**4c**) (1.2 g, 34%) as an oil (Found: C, 72.3; H, 10.9. $C_{17}H_{30}O_3$ requires C, 72.3; H, 10.7%); R_F (diethyl ether) 0.40; $\nu_{max.}$ 3 430 (OH) and 1 030 cm^{-1} (O–CH–O); δ_H (80 MHz) 4.6 (1 H, m, O–CH–O) 3.2—4.1 (6 H, m, 3 × CH_2O), 1.3—2.5 (16 H, m), 1.25 (3 H, s, CH_3), 1.1 (3 H, s, CH_3), and 0.8 (1 H, d, *J* 9 Hz, H*).

(1S,2R,3S,5R)-3-*Acetoxymethyl*-6,6-*dimethyl*-2-[2-(*tetrahydropyran*-2-*yloxy*)*ethyl*]*bicyclo*[3.1.1]*heptane* (**4d**).—Acetyl chloride (0.3 ml, 0.33 g, 4.2 mmol) was added dropwise to a stirred mixture of the alcohol (**4c**) (0.90 g, 3.2 mmol) and pyridine (0.64 ml, 0.63 g, 7.9 mmol) in diethyl ether (16 ml) at such a rate as to maintain a gentle reflux. The mixture was stirred under reflux for 1 h, then cooled and filtered. The filtrate was washed with aqueous copper sulphate (2%; 15 ml), dried ($MgSO_4$), and concentrated under reduced pressure to give a brown oil (1.3 g). The crude product was purified by l.p.l.c. on a column of silica gel (85 g, 3.4 × 20 cm) using diethyl ether as eluant to give the *acetoxy compound* (**4d**) (0.78 g, 75%) as an oil (Found: C, 70.3; H, 10.0%; M^+, 324. $C_{19}H_{32}O_4$ requires C, 70.3; H, 9.9%, *M*, 324); R_F [diethyl ether–light petroleum (b.p. 60—80 °C) (1:1)] 0.50; $\nu_{max.}$ 1 738 ($OCOCH_3$) and 1 030 cm^{-1} (O–C–O); δ_H (80 MHz) 4.6 (1 H, m, OCHO), 3.2—4.1 (6 H, m, 3 × CH_2O), 1.3—2.5 (18 H, m), 1.25 (3 H, s, CH_3), 1.0 (3 H, s, CH_3), and 0.8 (1 H, d, *J* 9 Hz, H*).

(1S,2R,3S,5R)-3-*Acetoxymethyl*-2-(2-*hydroxyethyl*)-6,6-*dimethylbicyclo*[3.1.1]*heptane* (**11a**).—A mixture of the acetoxy compound (**4d**) (0.7 g, 2.2 mmol) and acetic acid–water (2:1; 24 ml) was stirred at 40—44 °C for 2 h, cooled, diluted with water (50 ml), and extracted with diethyl ether (150 ml). The extract was washed with water (3 × 50 ml), dried ($MgSO_4$), and concentrated under reduced pressure to give the *acetoxy alcohol* (**11a**) (0.46 g, 89%) as a yellow oil (Found: C, 70.1; H, 10.1. $C_{14}H_{24}O_3$ requires C, 69.96; H, 10.07%); R_F (diethyl ether) 0.30; $\nu_{max.}$ 3 440 (OH) and 1 738 cm^{-1} ($OCOCH_3$); δ_H (60 MHz) 4.0 (2 H, d, *J* 5.5 Hz, CH_2OAc), 3.67 (2 H, t, *J* 7 Hz, CH_2OH), 1.5—2.5 (13 H, m, one exchangeable H), 1.2 (3 H, s, CH_3), and 0.8 (1 H, d, *J* 9 Hz, H*).

* This is the 7-β-H of the pinane ring.

(1S,2R,3S,5R)-3-*Acetoxymethyl*-2-*formylmethyl*-6,6-*dimethylbicyclo*[3.1.1]*heptane* (**11b**).—A solution of the acetoxy alcohol (**11a**) (238 mg, 1.0 mmol) in dried dichloromethane (6 ml) was added in one portion to a stirred suspension of pyridinium chlorochromate (330 mg, 1.67 mmol) in dry dichloromethane (6 ml) and after 1.5 h the reaction mixture was diluted with anhydrous diethyl ether (25 ml) and filtered. The filtrate was concentrated under reduced pressure to give the aldehyde (**11b**) (220 mg, 93%) as a light brown oil, R_F (diethyl ether) 0.45; $\nu_{max.}$ 2 720 (CHO), 1 738 ($OCOCH_3$), and 1 720 cm^{-1} (CHO); δ_H (80 MHz) 9.7 (1 H, t, *J* 1.5 Hz, CHO), 4.0 (2 H, d, *J* 7 Hz, CH_2OAc), 1.3—2.7 (12 H, m), 1.2 (3 H, s, CH_3), 1.05 (3 H, s, CH_3), and 0.8 (1 H, d, *J* 9 Hz, H*).

(1S,2R,3S,5R)-2-[(Z)-6-*Carboxyhex*-2-*enyl*]-3-*hydroxymethyl*-6,6-*dimethylbicyclo*[3.1.1]*heptane* (**12**).—A stirred suspension of (4-carboxybutyl)triphenylphosphonium bromide (1.48 g, 3.4 mmol) in dried THF (30 ml) under argon was treated with a solution of potassium t-butoxide (0.94 g, 8.4 mmol) in dried THF (20 ml) at room temperature. After the mixture had been stirred for 20 min a solution of the aldehyde (**11b**) (0.20 g, 0.84 mmol) in dried THF (5 ml) was added. The mixture was stirred for 2.5 h, water (11.4 ml) was then added, and the mixture was stirred for a further 0.5 h. The reaction mixture was then diluted with water (100 ml) and washed with diethyl ether (50 ml), and the aqueous phase was acidified to pH 2 using aqueous hydrochloric acid (2M) and then extracted with diethyl ether (2 × 40 ml). The combined extracts were dried ($MgSO_4$) and concentrated under reduced pressure to give the acid (**12**) (0.21 g, 89%) [Found: *m*/*z* 280 (M^+), 262 ($M - H_2O$)$^+$, 249 ($M - CH_2OH$)$^+$, and 235 ($M - CO_2H$)$^+$]; R_F (diethyl ether) 0.37; $\nu_{max.}$ 2 600—3 400 (CO_2H) and 1 710 cm^{-1} (CO_2H); δ_H (80 MHz) 5.35 (2 H, m, CH=CH), 4.6 (2 H, m, 2 × OH, exchangeable), 3.55 (2 H, m, CH_2OH), 1.3—2.6 (15 H, m), 1.2 (3 H, s, CH_3), 1.05 (3 H, s, CH_3), and 0.8 (1 H, d, *J* 9.5 Hz, H*).

(1S,2R,3S,5R)-3-(*Hydroxymethyl*)-2-[(Z)-6-*methoxycarbonylhex*-2-*enyl*]-6,6-*dimethylbicyclo*[3.1.1]*heptane* (**13a**).—A solution of the acid (**12**) (0.31 g, 1.1 mmol) in diethyl ether (5 ml) was treated with an excess of an ethereal solution of diazomethane. After 1 h the excess of diazomethane was destroyed by the addition of acetic acid. The reaction mixture was washed with saturated aqueous sodium hydrogen carbonate (15 ml), dried (Na_2SO_4), and concentrated under reduced pressure to give the *hydroxy ester* (**13a**) (0.3 g, 92%) as a yellow oil (Found: C, 73.2; H, 10.7%; M^+, 294. $C_{18}H_{30}O_3$ requires C, 73.4; H, 10.3%; *M*, 294); R_F [diethyl ether–n-hexane (3:7)] 0.11; $\nu_{max.}$ 3 440 (OH) and 1 740 cm^{-1} (CO_2R); δ_H (60 MHz) 5.4 (2 H, m, CH=CH), 3.7 (3 H, s, CO_2CH_3), 3.55 (2 H, m, CH_2OH), 1.3—2.7 (16 H, m, one exchangeable H), 1.2 (3 H, s, CH_3), 1.05 (3 H, s, CH_3), and 0.8 (1 H, d, *J* 9 Hz, H*).

(1S,2R,3S,5R)-3-*Formyl*-2-[(Z)-6-*methoxycarbonylhex*-2-*enyl*]-6,6-*dimethylbicyclo*[3.1.1]*heptane* (**13b**).—A solution of the hydroxy ester (**13a**) (100 mg, 0.36 mmol) in dried dichloromethane (2.5 ml) was added in one portion to a stirred suspension of pyridinium chlorochromate (120 mg, 0.6 mmol) in dried dichloromethane (2.5 ml) and after 1.5 h the reaction mixture was diluted with anhydrous diethyl ether (15 ml) and filtered. The filtrate was concentrated under reduced pressure to give the formyl ester (**13b**) (95 mg, 95%) as a light brown oil, R_F (diethyl ether) 0.57; $\nu_{max.}$ 2 710 (CHO) and 1 740 cm^{-1} (CO_2CH_3); δ_H (80 MHz) 9.6 (1 H, d, *J* 2 Hz, CHO), 5.35 (2 H, m, CH=CH), 3.7 (3 H, s, CO_2CH_3), 1.4—3.0 (15 H, m), 1.25 (3 H, s, CH_3), 1.05 (3 H, s, CH_3), and 0.7 (1 H, d, *J* 9 Hz, H*).

(1S,2R,3R,5S)-2-[(Z)-6-*Methoxycarbonylhex-2-enyl*]-6,6-*dimethyl*-3-[(E)-3-*oxo*-4-*phenoxybut*-1-*enyl*]*bicyclo*[3.1.1]*heptane* (**15**).—A stirred solution of the lithium salt of dimethyl (2-oxo-3-phenoxypropyl)phosphonate, (**14**),[10] (125 mg, 0.47 mmol) in dried THF (2.5 ml) was treated with a solution of the formyl ester (**13b**) (110 mg, 0.78 mmol) in dry THF (2.5 ml). After 24 h the reaction mixture was concentrated under reduced pressure, diluted with water (30 ml), and extracted with diethyl ether (3 × 40 ml). The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure to give a yellow oil (150 mg) which was purified by l.p.l.c. on a column of silica gel (12 g, 2.4 × 11 cm) and eluted with diethyl ether–n-hexane (1:1) to give the phenoxy keto ester (**15**) (110 mg, 33%) as an oil (Found: M^+, 424. Calc. for $C_{27}H_{36}O_4$ *M*, 424); R_F [diethyl ether–n-hexane (1:1)] 0.41; $\nu_{max.}$ 1 740 (C=O), 1 695 (conj. C=O), 1 625 (conj. C=C), 1 600, and 1 500 cm^{-1} (arom.); $\lambda_{max.}$ EtOH 219 (ε 15 000), 235 (11 500), 268 (2 900), and 278 nm (1 800); δ_H (80 MHz) 7.4—6.8 (6 H, m, C*H*=CH–C=O and Ph), 6.3 (1 H, d, *J* 16 Hz, CH=C*H*–C=O), 5.3 (2 H, m, CH=CH), 4.7 (2 H, m, CH_2O) 3.65 (3 H, s, CO_2CH_3), 0.7—2.75 (22 H, m), 1.2 (3 H, s, CH_3), 1.05 (3 H, s, CH_3), and 0.84 (1 H, d, *J* 9 Hz, H*).

(1S,2R,3R,5S)-3-[(E)-3-*Hydroxy*-4-*phenoxybut*-1-*enyl*]-2-[(Z)-6-*methoxycarbonylhex*-2-*enyl*]-6,6-*dimethylbicyclo*-[3.1.1]*heptane* (**16**).—A solution of L-selectride (1M; 0.28 ml, 0.28 mmol) in THF was added dropwise to a stirred solution of the keto ester (**15**) (0.10 g, 0.24 mmol) in dried THF (2.5 ml) at −75 °C under argon. After 0.5 h acetone (1 ml) was added to the reaction mixture and the temperature was allowed to rise to 0 °C. A cold mixture of aqueous sodium hydroxide (3M; 0.5 ml) and aqueous hydrogen peroxide (30%; 0.5 ml) was added cautiously during 5 min, keeping the reaction mixture temperature at 0 °C. Aqueous sulphuric acid (2M) was added dropwise until the pH of the reaction mixture was 6. The reaction mixture was then briefly concentrated under reduced pressure to remove the THF, then saturated with sodium chloride and extracted with diethyl ether (3 × 10 ml). The combined extracts were washed in turn with water (40 ml) and saturated aqueous sodium chloride (40 ml) and dried ($MgSO_4$) and concentrated under reduced pressure to give the *hydroxy ester* (**16**) (90 mg, 89%) as a yellow oil. A sample was purified by p.l.c. [silica gel; diethyl ether–n-hexane (1 : 1); 20 × 20 × 0.01 cm plates] (Found: C, 75.6; H, 9.1%; M^+, 426. $C_{27}H_{38}O_4$ requires C, 76.0; H, 8.98%; *M*, 426); R_F (diethyl ether) 0.51; $\nu_{max.}$ 3 440 (OH), 1 740 (C=O), 1 600, 1 500 (arom.), 975 (C=C), and 755 cm^{-1} (arom.); δ_H (80 MHz) 7.5—6.8 (5 H, m, Ph), 5.9—5.25 (4 H, m, 2 × CH=CH), 3.88 (2 H, m, CH_2O), 3.65 (3 H, s, CO_2CH_3), and 0.7—2.75 (23 H, m).

(1S,2R,3R,5S)-3-[(E)-3-(*t-Butyldimethylsilyloxy*)*oct*-1-*enyl*]-2-*formyl*-6,6-*dimethylbicyclo*[3.1.1]*heptane* (**19a** *and* **b**).—A stirred solution of (*E*)-3-(t-butyldimethylsilyloxy)-1-iodo-oct-1-ene (0.67 g, 1.8 mmol) in dried diethyl ether (12 ml) under argon at −78 °C was treated with t-butyl-lithium (1.8M; 2 ml, 3.6 mmol) in pentane and the mixture was stirred for 2 h. Hexamethylphosphorous triamide (0.7 ml, 3.8 mmol) was added to a stirred suspension of pentynyl copper[8] (0.25 g, 1.9 mmol) in dried diethyl ether (5 ml) under argon and the mixture was stirred until the solution became clear (*ca.* 15 min). The solution of the copper complex was then added dropwise to the lithium salt reaction mixture, followed after 0.25 h by a solution of myrtenal (**17**) (0.25 g, 1.7 mmol) in dried diethyl ether (5 ml). The reaction mixture was kept at −75 °C for 2 h, and was then warmed to −4 °C, stirred for 0.75 h, and added to aqueous ammonium sulphate (20% w/v; 50 ml) at 0 °C. The aqueous phase was washed with diethyl ether (2 × 50 ml) and the combined organic material was treated with sulphuric acid (2% v/v; 50 ml) and filtered through Celite. The separated organic material was washed with aqueous sodium hydrogen carbonate (5% w/v; 50 ml), dried (Na_2SO_4), and concentrated under reduced pressure to give a brown oil (0.56 g). A sample of the oil (0.2 g) was purified by p.l.c. [silica gel, 20 × 20 × 0.1 cm plates; ethyl acetate–cyclohexane–formic acid (40:40:1)] to give the *aldehyde* (**19a** and **b**) (0.13 g, 58%) as an oil (Found: C, 73.4; H, 11.6%; M^+, 392 (weak). $C_{24}H_{44}O_2Si$ requires C, 73.4; H, 11.29%; *M*, 392); R_F [diethyl ether–ethyl acetate–n-hexane (3:1:1)] 0.64; $\nu_{max.}$ 2 700, 1 730 (CHO), 1 260 [$Si(CH_3)_2$], and 970 cm^{-1} (C=C); δ_H (60 MHz) 9.63 (1 H, m, CHO), 5.5 (2 H, m, CH=CH), 4.0 (1 H, m, C*H*OSi), 1.0—2.8 (19 H, m), 0.88 [12 H, m, $SiC(CH_3)_3$ and CH_2CH_3), 0.75 (3 H, s, CH_3), and 0.05 [6 H, s, $Si(CH_3)_2$].

(1S,2R,3R,5S)-3-[(E)-3-(*t-Butyldimethylsilyloxy*)*oct*-1-*enyl*]-2-(2-*methoxyvinyl*)-6,6-*dimethylbicyclo*[3.1.1]*heptane* (**20a** *and* **b**).—To a stirred solution of butyl-lithium (1.6M; 14.2 ml, 22.7 mmol) in n-hexane under nitrogen at −78 °C was added a solution of di-isopropylamine (4.65 ml, 33.6 mmol) in dried THF (50 ml). After 0.5 h the solution was added dropwise to a stirred suspension of methoxymethyl(triphenyl)phosphonium chloride (7.40 g, 21.6 mmol) in dried THF (50 ml) at −75 °C under nitrogen. The mixture was stirred for 0.5 h and then allowed to warm to 0 °C during 0.5 h, and a solution of the aldehyde (**19a** and **b**) (3.0 g, 7.6 mmol) in dried THF (50 ml) was added dropwise. The mixture was stirred for 2 h and then concentrated under reduced pressure at 40 °C. The residue was dissolved in water (100 ml) and extracted with diethyl ether (2 × 100 ml). The combined extracts were dried ($MgSO_4$) and concentrated under reduced pressure to give a dark brown oil (4 g) which was purified by chromatography on a silica gel column (3.4 × 26 cm) with diethyl ether–n-hexane (1 : 4) as eluant to give the *vinyl ether* (**20a** and **b**) (1.4 g, 44%) as a pale yellow oil (Found: C, 74.2; H, 11.8%; M^+, 420. $C_{26}H_{48}O_2Si$ requires C, 74.2; H, 11.5%; *M*, 420); R_F [diethyl ether–ethyl acetate–n-hexane (3:1:1)] 0.69; $\nu_{max.}$ 1 670, 1 650 (C=C–OCH_3), 1 260 [$Si(CH_3)_2$], and 980 cm^{-1} (C=C); δ_H (60 MHz) 4.7—6.45 (4 H, m, 2 × HC=CH), 3.8—4.2 (1 H, m, CHOSi), 3.5 and 3.45 (together 3 H, 2 s, *cis*- and *trans*-C=C–OCH_3), 0.9—2.6 (22 H, m), 0.85 [12 H, m, $SiC(CH_3)_3$ and CH_2CH_3], and 0.03 [6 H, s, $Si(CH_3)_2$].

(1S,2R,3R,5S)-3-[(E)-3-(*t-Butyldimethylsilyloxy*)*oct*-1-*enyl*]-2-*formylmethyl*-6,6-*dimethylbicyclo*[3.1.1]*heptane* (**21a** *and* **b**).—A stirred solution of the vinyl ether (**20a** and **b**) (1.3 g, 3.2 mmol) in a 1:10 mixture of water–THF (20 ml) was treated with mercury(II) acetate (3.0 g, 9.4 mmol) and after 15 min saturated aqueous potassium iodide (40 ml) was added. After 5 min the reaction mixture was extracted with diethyl ether (2 × 40 ml) and the combined extracts were dried (Na_2SO_4) and concentrated under reduced pressure to give a yellow oil (2 g) which was purified by l.p.l.c. on a silica gel (80 g) column (2.4 × 23 cm) with diethyl ether–n-hexane (1:4) as eluant to give the aldehyde (**21a** and **b**) (0.77 g, 61%) as a pale yellow oil (Found: M^+, 406. Calc. for $C_{25}H_{46}O_2Si$: *M*, 406); R_F [diethyl ether–ethyl acetate–n-hexane (3:1:1)] 0.70; $\nu_{max.}$ 2 700 (CHO), 1 725 (CHO), 1 260 $Si(CH_3)_2$, and 980 cm^{-1} (C=C); δ_H (80 MHz) 9.7 (1 H, m, CHO), 5.4 (2 H, m, CH=CH), 4.05 (1 H, m, CHOSi), 0.9—2.7 (24 H, m), 0.85 [12 H, m, $SiC(CH_3)_3$ and CH_2CH_3], and 0.01 [6 H, s, $Si(CH_3)_2$].

(1S,2R,3R,5S)-3-[(E)-3-(t-*Butyldimethylsilyloxy*)*oct*-1-*enyl*]-2-[(Z)-6-*carboxyhex*-2-*enyl*]-6,6-*dimethylbicyclo*[3.1.1]-*heptane* (**22a** *and* **b**).—A stirred suspension of (4-carboxybutyl)-triphenylphosphonium bromide (1.04 g, 2.4 mmol) in dried

* This is the 7-β-H of the pinane ring.

THF (20 ml) under argon at room temperature was treated with a solution of potassium t-butoxide (0.66 g, 5.9 mmol) in dried THF (16 ml). The mixture was stirred for 20 min and then treated with a solution of the aldehyde (**21a** and **b**) (0.24 g, 0.59 mmol) in dried THF (4 ml). After 2.5 h water (8 ml) was added and the reaction mixture was stirred for a further 0.5 h. The reaction mixture was washed with diethyl ether (20 ml) and the ether phase was washed with saturated aqueous sodium hydrogen carbonate (20 ml). The combined aqueous material was acidified to pH 2 using dil. hydrochloric acid, and extracted with diethyl ether (2 × 30 ml). The combined extracts were dried (Na_2SO_4) and concentrated under reduced pressure to give the acid (**22a** and **b**) (0.125 g) as a yellow oil which was used without purification, R_F [ethyl acetate–cyclohexane–formic acid (40:40:1)] 0.64; $\nu_{max.}$ 2 600—3 600, 1 715 (CO_2H), and 980 cm^{-1} (C=C); δ_H (80 MHz) 5.3 (4 H, m, 2 × CH=CH), 3.95 (1 H, m, CHOSi), 3.0 (1 H, br, OH, exchangeable), 0.6—2.6 (42 H, m), and 0.12 [6 H, s, $Si(CH_3)_2$].

(1S,2R,3R,5S)-2-[(Z)-6-*Carboxyhex*-2-*enyl*]-3-[(*E*)-3-*hydroxyoct*-1-*enyl*]-6,6-*dimethylbicyclo*[3.1.1]*heptane* (**2a** *and* **b**).—A solution of the acid (**22a** and **b**) (0.125 g, 0.26 mmol) in a mixture of glacial acetic acid, water, and THF (65 : 35 : 10; 4 ml) was stirred at 40—45 °C for 3 h. The reaction mixture was then diluted with diethyl ether (20 ml) and water (20 ml) and the organic layer was separated and washed with water (20 ml) several times until the pH of the washings was 4. The ethereal solution was dried ($MgSO_4$) and concentrated under reduced pressure to give a yellow oil (90 mg) which was purified by p.l.c. (silica gel, 20 × 20 × 0.1 cm plate), developer ethyl acetate–cyclohexane–formic acid (40:40:1), to give the *hydroxy acids* (**2a** and **b**) (30 mg, 31% over the last two stages) as an oil (Found: C, 76.2; H, 10.9. $C_{24}H_{40}O_3$ requires C, 76.55; H, 10.7%); R_F [ethyl acetate–cyclohexane–formic acid (40:40:1)] 0.63 and 0.68; $\nu_{max.}$ 2 400—3 600 (CO_2H), 1 710 (CO_2H), and 970 cm^{-1} (C=C); δ_H (80 MHz) 5.5 (4 H, m, 2 × CH=CH), 4.7 (2 H, m, 2 × OH, exchangeable), 4.1 (1 H, m, C*H*OH), and 0.5—2.5 (33 H, m).

(1S,2R,3R,5S)-3-[(E,3S)-3-(*t-Butyldimethylsilyloxy*)*oct*-1-*enyl*]-2-*formyl*-6,6-*dimethylbicyclo*[3.1.1]*heptane* (**19a**).—Following the procedure for the preparation of (**19a** and **b**), (1*R*,5*S*)-2-formyl-6,6-dimethylbicyclo[3.1.1]hept-2-ene (myrtenal) (**17**) (0.43 g, 2.9 mmol) was treated with the resolved lithium cuprate reagent prepared as before from (1*E*,3*S*)-3-(t-butyldimethylsilyloxy)-1-iodo-oct-1-ene (1.17 g, 3.2 mmol), t-butyl-lithium (2M; 3.12 ml, 6.24 mmol) in n-pentane, and hexamethylphosphorous triamide (1.2 ml, 6.5 mmol) to give a brown oil (1.16 g) which was purified by l.p.l.c. on a column (2.4 × 15 cm) of silica gel (16 g) using diethyl ether–n-hexane (5:95) as eluant to give the aldehyde (**19a**) (0.42 g, 54%) as an oil with the same spectral properties (i.r., n.m.r., m.s.) as those of the aldehyde mixture (**19a** and **b**).

(1S,2R,3R,5S)-3-[(E,3S)-3-(*t-Butyldimethylsilyloxy*)*oct*-1-*enyl*]-2-(2-*methoxyvinyl*)-6,6-*dimethylbicyclo*[3.1.1]*heptane* (**20a**).—Following the procedure for the preparation of (**20a** and **b**), the aldehyde (**19a**) (0.33 g, 0.84 mmol) was treated with the ylide generated using n-butyl-lithium (1.6M; 1.7 ml, 2.5 mmol) in n-pentane, di-isopropylamine (0.50 ml, 3.6 mmol), and methoxymethyl(triphenyl)phosphonium chloride (0.83 g, 2.4 mmol) to give the vinyl ether (**20a**) (0.33 g, 93%) as a light yellow oil with the same spectral properties (i.r., n.m.r., m.s.) as those of the mixture (**20a** and **b**).

(1S,2R,3R,5S)-3-[(E,3S)-3-(*t-Butyldimethylsilyloxy*)*oct*-1-*enyl*]-2-*formylmethyl*-6,6-*dimethylbicyclo*[3.1.1]*heptane* (**21a**).—Following the procedure for the preparation of (**21a** and **b**), a solution of the vinyl ether (**20a**) (0.12 g, 0.28 mmol) in THF–water (10:1, 1.6 ml) was treated with mercury(II) acetate (0.27 g, 0.85 mmol) and then, after 15 min, saturated aqueous potassium iodide (3.6 ml) was added to give the aldehyde (**21a**) (0.11 g, 95%) as a yellow oil with the same spectral properties (i.r., n.m.r., m.s.) as those of the aldehyde mixture (**21a** and **b**).

(1S,2R,3R,5S)-2-[(Z)-6-*Carboxyhex*-2-*enyl*]-3-[(E,3S)-3-*hydroxyoct*-1-*enyl*]-6,6-*dimethylbicyclo*[3.1.1]*heptane* (**2a**).—Following the procedure for the preparation of (**22a** and **b**), the aldehyde (**21a**) (70 mg, 0.17 mmol) was added to the ylide generated by treating (4-carboxybutyl)triphenylphosphonium bromide (0.30 g, 0.69 mmol) with potassium t-butoxide (0.19 g, 1.7 mmol) in THF. The crude product (**22a**) was then hydrolysed following the same procedure as for the preparation of (**2a** and **b**) to give PTA_2 (**2a**) (24.3 mg, 38%).

(1S,2R,3R,5S)-2-*Carboxymethyl*-3-[(E,3S)-3-*hydroxyoct*-1-*enyl*]-6,6-*dimethylbicyclo*[3.1.1]*heptane* (**6a**).—A stirred solution of the aldehyde (**21a**) (65 mg, 0.16 mmol) in dried DMF (1 ml) at room temperature was treated with pyridinium dichromate (0.12 g, 0.32 mmol) and then stirred for 6 h. The reaction mixture was added to water (20 ml) and extracted with diethyl ether (2 × 20 ml). The combined extracts were concentrated under reduced pressure and the crude product (**25**) was hydrolysed following the same procedure as for the preparation of (**2a** and **b**) to give the acid (**6a**) (8.0 mg, 16%).

(1S,2R,3R,5S)-2-*Formyl*-3-[(E)-*hept*-1-*enyl*]-6,6-*dimethylbicyclo*[3.1.1]*heptane* (**24a**).—A stirred solution of (*E*)-1-iodohept-1-ene[10] (3.4 g, 15.2 mmol) in dried diethyl ether (30 ml) under argon at −78 °C was treated with t-butyl-lithium (2M; 15 ml, 30 mmol) in n-pentane and the mixture was stirred for 2 h at −78 °C.

Hexamethylphosphorous triamide (5.8 ml, 31 mmol) was added to a stirred suspension of pentynylcopper (2.07 g, 14.3 mmol) in dried diethyl ether (30 ml) under argon and the mixture was stirred until the solution became clear (*ca.* 15 min). The clear solution of copper complex was then added dropwise to the vinyl-lithium solution at −78 °C and after 15 min a solution of myrtenal (**17**) (2.07 g, 13.8 mmol) in dried diethyl ether (15 ml) was added dropwise. After being stirred for 2 h at −75 °C the reaction mixture was warmed to −4 °C and the mixture was stirred for a further 0.75 h. The reaction mixture was then added to aqueous ammonium sulphate solution (20%; 300 ml) at 0 °C. After equilibration in a separatory funnel the (now blue) aqueous phase was separated and extracted with diethyl ether (2 × 300 ml). The combined ethereal phases were treated with aqueous sulphuric acid (2%; 300 ml) and the resultant mixture was filtered through Celite. The filtrate was separated and the organic phase was washed with aqueous sodium hydrogen carbonate (5%; 300 ml), dried ($MgSO_4$), and concentrated under reduced pressure to give a light brown oil (3.2 g) which was purified by l.p.l.c. on a silica gel column (120 g, 22 × 2.4 cm) using diethyl ether–n-hexane (5 : 95) eluant. This gave the aldehyde (**24a**) (2.2 g, 64%) as an oil, $\nu_{max.}$ 2 710 (CHO), 1 730 (CHO), and 970 cm^{-1} (C=C); R_F [diethyl ether–n-hexane (5:95)] 0.38; δ_H (60 MHz) 9.8 (1 H, s, CHO), 5.2—5.5 (2 H, m, CH=CH), and 0.6—3.7 (25 H, m).

(1S,2R,3R,5S)-3-[(E)-*Hept*-1-*enyl*]-2-(2-*methoxyvinyl*)-6,6-*dimethylbicyclo*[3.1.1]*heptane* (**24b**).—A stirred solution of n-butyl-lithium (1.2M; 16.7 ml, 20 mmol) in n-hexane under nitrogen at −78 °C was treated with a solution of di-isopropylamine (4.0 ml, 29 mmol) in dried THF (30 ml). After 0.5 h the solution was added dropwise to a stirred suspension of methoxymethyl(triphenyl)phosphonium chloride (6.7 g, 19.6 mmol) in dried THF (40 ml) at −75 °C. The mixture was stirred

for 0.5 h at −75 °C, allowed to warm to 0 °C during 0.5 h, and then a solution of the aldehyde (**24a**) (1.7 g, 6.84 mmol) in dried THF (30 ml) was added dropwise. The reaction mixture was stirred for 2 h and concentrated under reduced pressure at 40 °C. The residue was dissolved in water (100 ml) and extracted with diethyl ether (2 × 100 ml). The extracts were dried ($MgSO_4$) and concentrated under reduced pressure to give a brown oil (2.8 g) which was purified by chromatography (l.p.l.c.) on a silica gel column (120 g, 22 × 2.4 cm) using diethyl ether–n-hexane (5:95) as eluant. This gave the vinyl ether (**24b**) (1.2 g, 63%) as a pale yellow oil (Found: M^+, 276. Calc. for $C_{19}H_{32}O$: M, 276); $\nu_{max.}$ 1 645, 1 655 (C=C–OCH_3), and 965 cm^{-1} (C=C); R_F [diethyl ether–n-hexane (5:95)] 0.51.

(1S,2R,3R,5S)-2-*Formylmethyl*-3-[(E)-*hept*-1-*enyl*]-6,6-*dimethylbicyclo*[3.1.1]*heptane* (**24c**).—A stirred solution of the vinyl ether (**24b**) (0.90 g, 3.3 mmol) in a mixture of THF and water (10:1, 20 ml) was treated with mercury(II) acetate (3.27 g, 10.0 mmol) and, after 15 min, saturated aqueous potassium iodide (47 ml) was added. After 5 min the reaction mixture was extracted with diethyl ether (2 × 50 ml) and the extracts were dried (Na_2SO_4) and concentrated under reduced pressure to give the aldehyde (**24c**) (1.04 g) as a yellow oil, R_F (diethyl ether) 0.63; δ_H (80 MHz) 9.65 (1 H, t, J 3 Hz, CHO), 5.25 (2 H, m, CH=CH), 0.65—2.6 (29 H, m).

(1S,2R,3R,5S)-2-[(Z)-6-*Carboxyhex*-2-*enyl*]-3-[(E)-*hept*-1-*enyl*]-6,6-*dimethylbicyclo*[3.1.1]*heptane* (**24d**).—A stirred suspension of (4-carboxybutyl)triphenylphosphonium bromide (0.68 g, 1.5 mmol) in dried THF (10 ml) under argon was treated with a solution of potassium t-butoxide (0.44 g, 3.9 mmol) in dried THF (10 ml) at room temperature. The mixture was stirred for 20 min and then treated with a solution of the aldehyde (**24c**) (0.10 g, 0.38 mmol) in dried THF (2.7 ml). After 2.5 h water (5 ml) was added and the mixture was stirred for a further 0.5 h, washed with diethyl ether (20 ml), and the ether phase was extracted with saturated aqueous sodium hydrogen carbonate (20 ml). The combined aqueous material was acidified to pH 2 using aqueous hydrochloric acid (2M), and extracted with diethyl ether (2 × 30 ml). The combined extracts were dried (Na_2SO_4) and concentrated under reduced pressure to give a brown oil (0.105 g) which was purified by p.l.c. [silica gel; ethyl acetate–cyclohexane–formic acid (40:40:1) (20 × 20 × 0.1 cm plate)] to give the *acid* (**24d**) (0.068 g, 51%) as an oil (Found: C, 79.9; H, 11.3. $C_{23}H_{38}O_2$ requires C, 79.7; H, 11.1%); R_F [ethyl acetate–cyclohexane–formic acid (40:40:1)] 0.62; $\nu_{max.}$ 2 600—3 400 (CO_2H), 1 710 (CO_2H), and 965 cm^{-1} (C=C); δ_H (60 MHz) 8.95 (1 H, m, CO_2H, exchangeable), 5.0—5.6 (4 H, m, 2 × CH=CH), and 0.7—2.7 (33 H, m).

(1S,2R,3R,5S)-2-*Carboxymethyl*-3-[(E)-*hept*-1-*enyl*]-6,6-*dimethylbicyclo*[3.1.1]*heptane* (**24e**).—A stirred solution of the aldehyde (**24c**) (0.080 g, 0.3 mmol) in dried DMF (1 ml) was treated with pyridinium dichromate (0.23 g, 0.6 mmol) at room temperature and, after 6 h, the mixture was diluted with water (20 ml) and extracted with diethyl ether (2 × 20 ml). The combined extracts were dried ($MgSO_4$) and concentrated under reduced pressure to give a yellow oil (0.103 g). The oil was purified by p.l.c. [silica gel; ethyl acetate–cyclohexane–formic acid (40:40:1) (20 × 0.1 cm plate)] to give the acid (**24e**) (20 mg, 24%) as a pale yellow oil, R_F [ethyl acetate–cyclohexane–formic acid (40:40:1)] 0.65; $\nu_{max.}$ 2 600—3 400, 1 708 (CO_2H), and 965 cm^{-1} (C=C); δ_H (60 MHz) 6.5 (1 H, m, CO_2H, exchangeable), 5.2—5.6 (2 H, m, CH=CH), and 0.7—2.7 (27 H, m).

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